T c a a a ac c a c c b a c a (TRACE-2): a a 3, c , -ab , a d dc d, - a

Y Wa , S aL, Y e Pa , Ha L, Ma W Pa , B ce C V Ca be , Lee H Sc a Ma c F e, Fe a C e, H Da, De a L, R L, J a Wa , Y Wa , X a Z a, Z a L, H a a Ze , Y X , Xa Me , e TRACE-I e a *

S a

Bac d T a a a

C , Ha a d M d ca Sc , B , MA, USA (Prof M Fisher MD); D a N , L Y P ' H a , L , C a (Prof F Che MD); D a N , L C a H a , L , C a (Prof H Dai MD); D a N , T C a P ' H a , T , C a (Prof D Li MD); D a N , C a H a A a d S a M d ca C , S a , C a (Prof R Li MD); D a N , S a T G a H a , Da , C a (Prof J Wang MD)

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a @ c c d. .c

See O for appendix

There has been a long debate about the appropriate dose of thrombolytics in Asian people with acute ischaemic stroke. The SITS-NEW study[7] aimed to evaluate the efficacy and safety of intravenous alteplase (0·9 mg/kg) as thrombolytic therapy within 3 h of onset of acute ischaemic stroke in an Asian population. This study showed the safety and efficacy of the standard dose of intravenous alteplase (0·9 mg/kg) in an Asian population, as previously observed in the European population studied in SITS-MOST.[8] Guidelines for intravenous thrombolysis in China,[1] Europe,[3] and the USA[2] all recommend the dose of 0·9 mg/kg. The ENCHANTED study,[9] which assessed low-dose (0·6 mg/kg) intravenous alteplase, did not meet the prespecified non-inferiority criteria for standard-dose intravenous alteplase. There is a paucity of data on the appropriate dosage, efficacy, and safety of tenecteplase as compared with alteplase in Asian populations with acute ischaemic stroke.

TRACE-1, a phase 2, dose-finding, randomised clinical trial in China showed tha-1.222 45 Tj 4.5 17MCID 266 /Lang (en-p020.787 -1.222 Td(TRACE-1, a phaseowevenous thromboly

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Ra d a a d a

Eligible participants were randomly assigned (1:1) to receive intravenous tenecteplase or alteplase. Block randomisation was done with the use of a central web-based randomisation system (Randomisation and Trial Supply Management version 3.1.2, Beijing Bioknow Information Technology, China) with a block length of four without stratification. The local investigators visited the web-randomisation system and obtained the random codes, and the treatment assignment was done according to the random code. All other treatments were guided by the standard of care for ischaemic stroke.

The intravenous thrombolytic treatment was open label. Evaluators for the clinical assessments and the independent clinical-event adjudication committee, which adjudicated primary and secondary efficacy endpoints and bleeding events, were blinded to treatment allocation.

P c d

Tenecteplase was given as a single, intravenous bolus (over 5–10 s) at a dose of 0·25 mg/kg of bodyweight (maximum dose 25 mg) immediately after randomisation. Intravenous alteplase was given at a dose of 0·9 mg/kg (maximum dose 90 mg), with 10% of the dose given as a bolus and the remainder over 1 h. Other treatments were carried out adhering to established clinical principles and medical practice guidelines. Participants who planned to undergo endovascular thrombectomy were excluded from the study. However, the recruited participants were not prohibited from subsequently receiving endovascular thrombectomy on the basis of the judgment of the treating neurologists or physicians. NCCT imaging or MRI was done to detect any haemorrhage at 24–36 h after randomisation.

Clinical assessments (including clinical symptoms, laboratory tests, and imaging data) were done at each site by trained and certified evaluators who were unaware of the trial group assignments at 24 h, 7 days or hospital discharge (whichever occurred first), and 90 days. The mRS score at 90 days was assessed in person or by telephone. The clinical events committee adjudicated the endpoint events on the basis of clinical symptoms, laboratory tests, and imaging data. Serious adverse events and adverse events were categorised according to standard terminology.

O c

The primary efficacy outcome was the proportion of participants with an excellent functional outcome, defined as an mRS score of 0–1 at 90 days. The secondary efficacy outcomes consisted of the proportion of patients with favourable functional outcomes (defined as an mRS score of 0–2 at 90 days); mRS score at 90 days; the proportion of patients with a substantial neurological improvement on the NIHSS (defined as a decrease of at least 4 points, a score no more than 1 at 24 h and at 7 days, or discharge, whichever occurred first); European health-related quality of life at 90 days; and the proportion of those with a Barthel Index score of at least 95 points at 90 days.

The primary safety outcome was the rate of symptomatic intracranial haemorrhage within 36 h defined by the European Cooperative Acute Stroke Study III.[12] Other safety outcomes included parenchymal haematoma 2 defined by the Safe Implementation of Thrombolysis in Stroke-Monitoring study;[8] any intracranial haemorrhage or other significant haemorrhagic event as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria;[13] and death from all causes within 90 days of disease onset. Both serious adverse events and adverse events were collected until 90 days. Definitions of outcomes are included in the protocol in the appendix (p 4).

S a ca a a

Based on a meta-analysis of previous trials, the risk ratio (RR) for the effect of alteplase versus placebo for the excellent functional outcome (mRS score of 0–1) was 1·24 (95% CI 1·14–1·36).[14] The non-inferiority boundary was defined to preserve at least 50% of the most conservative estimate of the efficacy of alteplase from the meta-analysis. The non-inferiority limit was calculated as exp(–1[(Log[1·14])/2])=0·937. Tenecteplase would be declared non-inferior if the lower 97·5% one-sided CI of the RR for the primary outcome did not cross 0·937 (corresponding to 3·74% absolute risk difference). Assuming a power of 85%, a one-sided α level of 0·025, and an absolute RR of 1·07 based on the phase 2 data (response rates of 63·64% for the tenecteplase group *vs* 59·32% for for the alteplase group),[10] the target sample size for each group was 643 patients. Allowing for a dropout rate of 10%, the final target sample size estimate was 1430 patients (715 in each treatment group).

Efficacy analyses were done in the modified intention-to-treat population and in the per-protocol population. The modified intention-to-treat population was defined as all randomly assigned participants who received the allocated thrombolytic; the per-protocol population was defined as all participants who completed the assigned treatment without major violation of the trial protocol or missing data for primary efficacy endpoints. A χ^2 test or Fisher's exact probability method was used for comparison of categorical variables, Wilcoxon rank sum test for comparison of ordinal variables, and *t* test or rank sum test for comparison of continuous variables. The Cochran-Mantel-Haenszel χ^2 test adjusting for the pooled-site effect (≥20 patients for each stratum) was used for comparison of primary endpoints between groups, and the 95% CI of RR was calculated. We used the normal approximation (Wald formula) to derive the 95% CI of absolute risk differences adjusting for the pooled-site effect. Odds ratio (OR) with 95% CIs were

calculated using binary logistic regression. Non-inferiority would be established if the lower bound of the two-sided 95% CI of the RR for the primary outcome was greater than the predefined non-inferiority margin of 0·937. A superiority test in the modified intention-to-treat population was planned if non-inferiority was found. For secondary efficacy outcomes, a common OR with its 95% CI was calculated using ordinal logistic regression

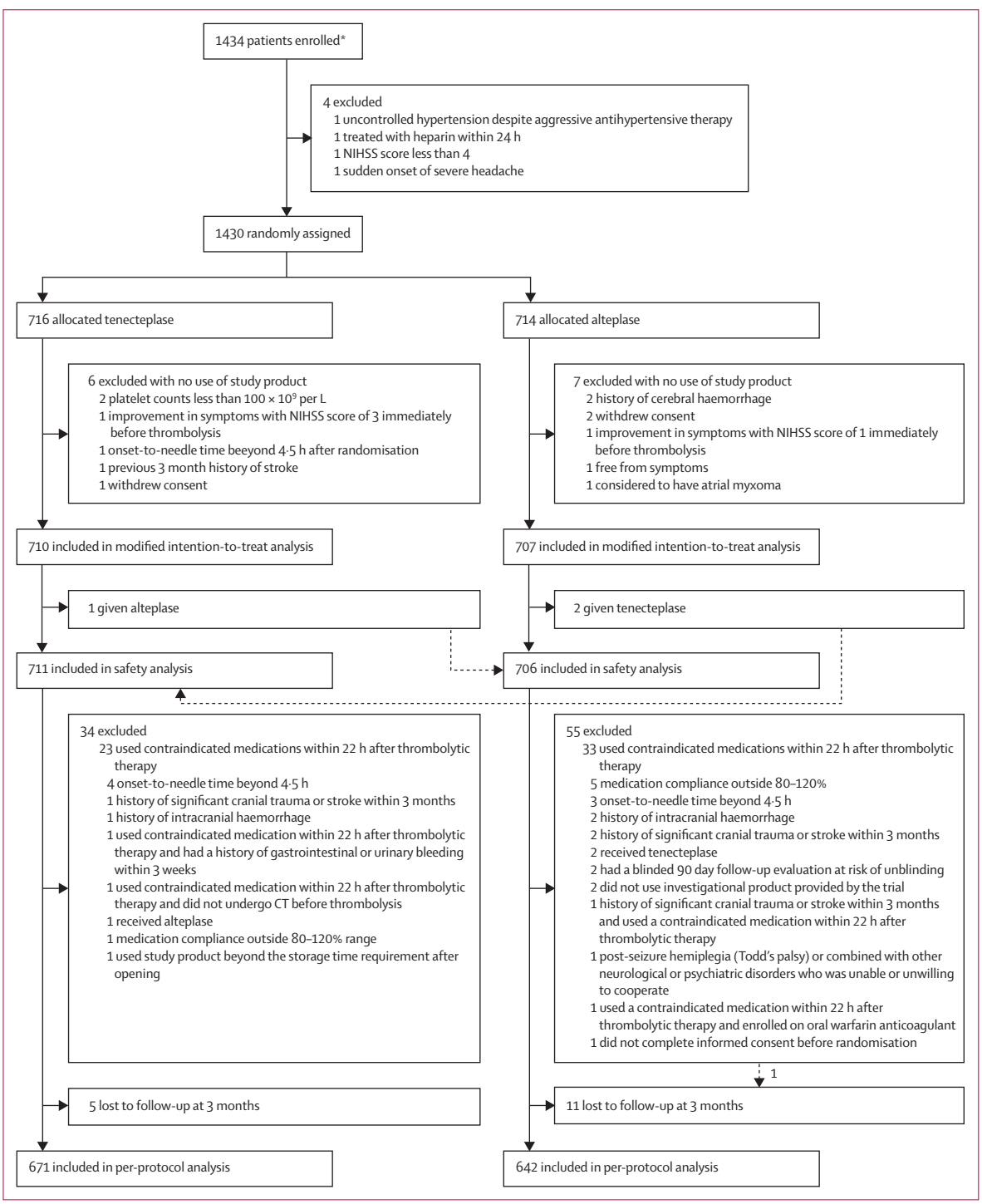

Figure 1: **E a d a d a**
NIHSS=National Institutes of Health Stroke Scale. *Physicians only obtained informed consent for this trial from patients who were suitable for intravenous thrombolytic but not for endovascular thrombectomy.

	T c a (=710)	A a (=707)
Age, years	67 (58–73)	65 (58–72)
Age		
18–59 years	211 (30%)	218 (31%)
60–79 years	423 (60%)	428 (61%)
≥80 years	76 (11%)	61 (9%)
Sex		
Male	492 (69%)	479 (68%)
Female	218 (31%)	228 (32%)
Ethnicity		
Chinese	710 (100%)	707 (100%)
Weight, kg	65 (59–75)	67 (60–75)
Medical history		
Hypertension	510 (72%)	512 (72%)
Diabetes	172 (24%)	207 (29%)
Hyperlipidaemia	130 (18%)	160 (23%)
Coronary heart disease	167 (24%)	166 (24%)
Arrhythmia	137 (19%)	146 (21%)
Current smoking		
Yes	266 (38%)	276 (39%)
No	443 (62%)	430 (61%)
Data missing	1 (<1%)	1 (<1%)
History of medication use		
Antiplatelet agents	90 (13%)	92 (13%)
Anticoagulant agents	5 (1%)	7 (1%)
Lipid-lowering drugs	67 (9%)	60 (9%)
Hypoglycaemic drugs	108 (15%)	118 (17%)
Antihypertensive drugs	296 (42%)	318 (45%)
mRS score before stroke		
0	634 (89%)	633 (90%)
1	76 (11%)	74 (11%)
(Continued from previous column)		
Baseline NIHSS score*	7 (5–10)	7 (6–10)
Baseline NIHSS score categories		
≤7	419 (59%)	387 (55%)
8–14	228 (32%)	261 (37%)
≥15	63 (9%)	59 (8%)
Onset-to-needle time, min	180 (135–222)	178·5 (135–230)
Onset-to-needle time categories, hours		
<3	353 (50%)	353 (50%)
≥3	357 (50%)	354 (50%)
Door-to-needle time, min	58 (45–78)	61 (48–84)
Bridging thrombectomy	27 (4%)	24 (3%)
Total costs, yuan†	11 255·45 (7537·13–16849·64)	12 094·25 (8039·37–17809·93)
Costs for thrombolysis, yuan	7376·00 (3688·00–7376·00)	5340·24 (5340·24–5340·24)
Duration of hospital stay		
≤7 days	125 (18%)	117 (17%)
>7 days	561 (79%)	574 (81%)
Data missing	24 (3%)	16 (2%)

Data are median (IQR) or n (%). NIHSS=National Institute of Health Stroke Scale. *NIHSS scores range from 0 to 42, with higher scores indicating more severe stroke. †Data available for 1360 patients (675 tenecteplase, 685 alteplase).

Table 1: **Ba c a ac c a c a d d - - a a**

for the ordinal 90-day mRS score, and ORs with their 95% CIs were calculated using the Cochran-Mantel-Haenszel method adjusting for the pooled-site effect for other secondary efficacy outcomes. The complete data were used to perform the main efficacy analyses without imputation for missing data. In sensitivity analysis, multiple imputation by fully conditional specification logistic regression was done to impute the missing data of the primary efficacy outcome. We used the Breslow-Day test to examine the heterogeneity of treatment effects across prespecified subgroups of bridging thrombectomy. Post-hoc subgroup analyses were also done for subgroups of sex, bridging thrombectomy, age, NIHSS, and onset-to-needle time.

Safety analyses were done in the safety analysis population, defined as all participants who received at least some of the study drug and had a safety assessment available. ORs were calculated with their 95% CIs using binary logistic regression. For comparison of adverse events and serious adverse events, χ^2 or Fisher's exact test were done, as appropriate.

A single primary efficacy variable was defined for this study and therefore there were no requirements to adjust for multiple comparisons in this study and no adjustment for multiple testing was done for secondary outcomes. No interim analysis was planned in this trial. An independent data-monitoring committee reviewed the safety data regularly and assessed whether the study should continue. All statistical analyses were done with use of SAS software (version 9.4).

The trial is registered with ClinicalTrials.gov, NCT04797013.

R d c

The trial drugs, tenecteplase and alteplase, were provided free of charge to the trial sites by China Shijiazhuang Pharmaceutical Company Recomgen Pharmaceutical (Guangzhou), which was the sponsor of this trial but had no role in design, conduct, and report of the trial. The investigators were responsible for data collection and conduct of the trial. The database was managed by the independent Giant contract research organisation. The statistical and data management centre at the China National Clinical Research Center for Neurological Diseases was responsible for the statistical analysis. The sponsors of the study had no role in study design, data collection, data analysis, data

interpretation, or writing of the report. The responsibility for submission was that of the corresponding author, agreed by the trial steering committee.

R

Recruitment took place between June 12, 2021, and May 29, 2022. Physicians only obtained informed consent for this trial from patients who were suitable for intravenous thrombolytic but not for endovascular thrombectomy. 1434 patients were screened after written informed consent and 4 were ineligible. 1430 patients with ischaemic stroke were enrolled at 53 clinical sites in China (appendix pp 5–6), of whom 716 were assigned to receive tenecteplase and 714 to receive alteplase (figure 1). All enrolled participants were Chinese. Six participants in the tenecteplase group and seven in the alteplase group did not receive the study drug and were excluded from the modified intention-to-treat analysis; the modified intention-to-treat population therefore included 710 participants allocated to the tenecteplase group and 707 to the alteplase group. The safety analysis set had 711 in the tenecteplase group and 706 in the alteplase group as two patients randomised to alteplase were given tenecteplase, and one patient randomised to tenecteplase was given alteplase; patients were classified according to the real treatment. The characteristics of the patients at baseline were similar between the two groups (table 1). The median age of the patients was 66 years (IQR 58–73), 68·5% were men and 31·5% were women. The median baseline NIHSS score was 7 (IQR 6–10) across all participants and the median time from stroke onset to treatment was 180 min (IQR 135–222) in the tenecteplase group and 178·5 min (IQR 135–230) in the alteplase group. 34 tenecteplase-treated and 55 alteplase-treated participants were excluded from the per-protocol analysis due to major deviation from protocol (appendix p 7). Five

tenecteplase-treated and 11 alteplase-treated participants (including one participant who did not meet the inclusion criteria) were lost to follow-up at 90 days with missing data for the primary outcomes; these participants were excluded from the per-protocol analysis. The concomitant medications used during hospital stay are presented in the appendix (p 8).

In the modified intention-to-treat analysis, 439 (62%) of 705 patients in the tenecteplase group and 405 (58%) of 696 patients in the alteplase group reached the primary outcome (mRS score of 0–1 at 3 months; RR 1·07, 95% CI 0·98 to 1·16; proportion difference 3·86, 95% CI –1·23 to 8·95; table 2, figure 2). The lower limit of the 95% CI of the RR was larger than the non-inferiority margin of 0·937 indicating that tenecteplase was non-inferior but not superior to alteplase. The sensitivity analysis with multiple imputation for missing data of the primary efficacy outcome showed similar results to the main analysis (appendix p 9). The proportion of patients with a favourable functional outcome (mRS score 0–2) in the tenecteplase group was 73% compared with 72% in the alteplase group (RR 1·01, 95% CI, 0·95–1·08). No

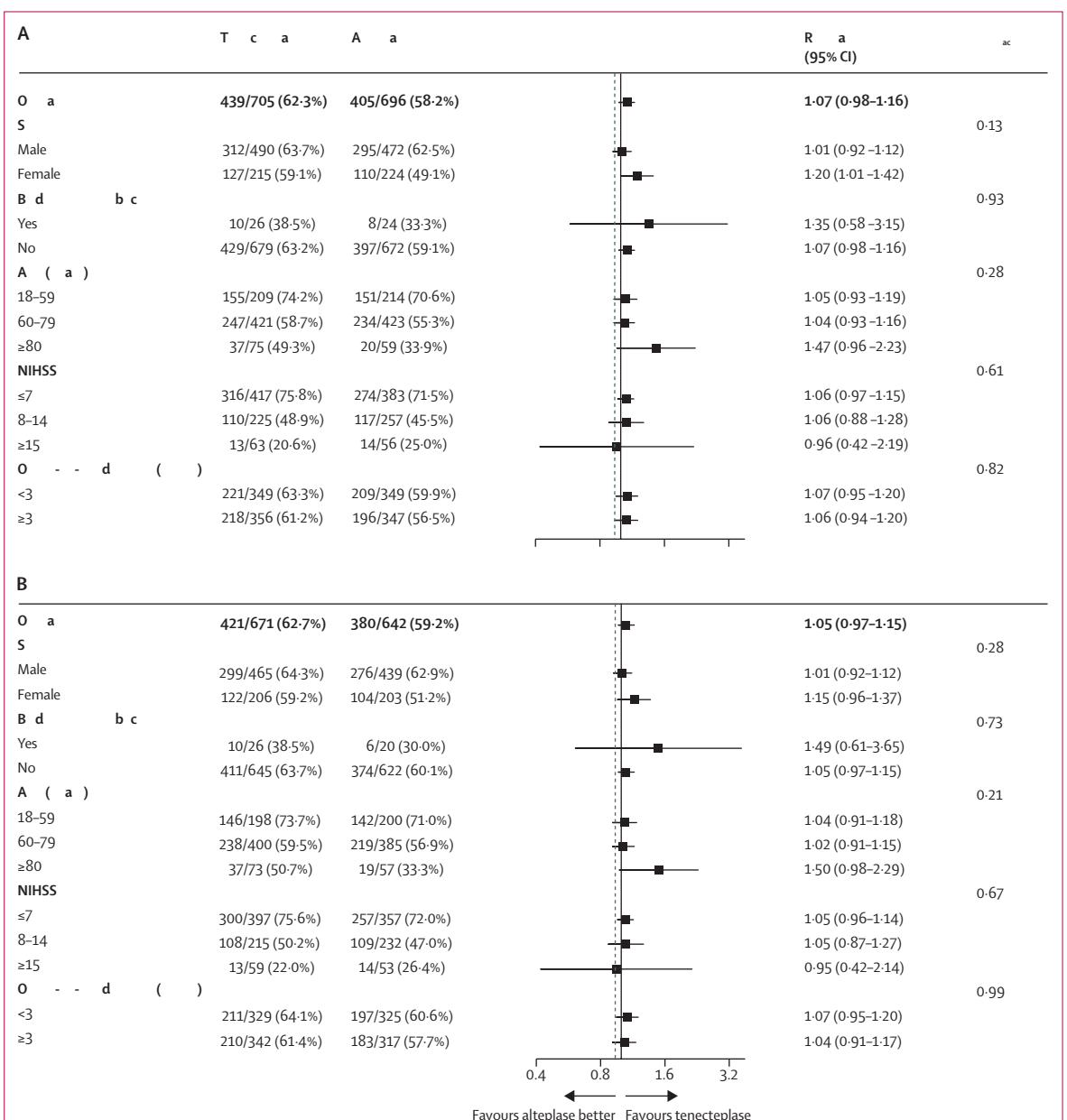

Figure 3: E c c a a c a d , a a a cac c c d b acc d d d - - a a (A) a d - c a (B)
The dashed vertical line indicates the non-inferiority limit of 0·937.

towards superior efficacy. Together with the results of other previous studies, 0·25 mg/kg (maximum dose of 25 mg) appears to be the optimal dosage for intravenous tenecteplase. Both the AcT and TRACE-2 trials used this dose of tenecteplase, and 0·9 mg/kg (maximum dose of 90 mg) alteplase was used as a comparison.

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